p53 Regulates Progenitor Cell Quiescence and Differentiation in the Airway.

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Authors: Alicia M McConnell, Changfu Yao, Alyson R Yeckes, Yizhou Wang, Anna S Selvaggio, Jie Tang, David G Kirsch, Barry R Stripp

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Public Summary:
Mechanisms that regulate progenitor cell quiescence and differentiation in slowly replacing tissues are not fully understood. In this study we show that the tumor suppressor protein Tp53 actively regulates epithelial cell quiescence and differentiation in the uninjured adult airway. Our findings reveal that Tp53 is an essential regulator of progenitor cell behavior, which shapes our understanding of stem cell quiescence during homeostasis and in cancer development.

Scientific Abstract:
Mechanisms that regulate progenitor cell quiescence and differentiation in slowly replacing tissues are not fully understood. Here, we demonstrate that the tumor suppressor p53 regulates both proliferation and differentiation of progenitors in the airway epithelium. p53 loss decreased ciliated cell differentiation and increased the self-renewal and proliferative capacity of club progenitors, increasing epithelial cell density. p53-deficient progenitors generated a pseudostratified epithelium containing basal-like cells in vitro and putative bronchioalveolar stem cells in vivo. Conversely, an additional copy of p53 increased quiescence and ciliated cell differentiation, highlighting the importance of tight regulation of p53 levels. Using single-cell RNA sequencing, we found that loss of p53 altered the molecular phenotype of progenitors and differentially modulated cell-cycle regulatory genes. Together, these findings reveal that p53 is an essential regulator of progenitor cell behavior, which shapes our understanding of stem cell quiescence during homeostasis and in cancer development.